Br J Clin Pharmacol 1998; **46**: 37–43

Pulmonary administration of aerosolised fentanyl: pharmacokinetic analysis of systemic delivery

Laurence E. Mather,[1] Annie Woodhouse,[1] M. Elizabeth Ward,[1] Stephen J. Farr,[2] Reid A. Rubsamen[2] & Lorne G. Eltherington[2]

[1]*Department of Anaesthesia and Pain Management, University of Sydney at Royal North Shore Hospital, St Leonards, NSW 2065, Australia and* [2]*Aradigm Corporation, 26219 Eden Landing Road, Hayward, CA 94545, USA*

Aims Pulmonary drug delivery is a promising noninvasive method of systemic administration. Our aim was to determine whether a novel breath-actuated, microprocessor-controlled metered dose oral inhaler (SmartMist™, Aradigm Corporation) could deliver fentanyl in a way suitable for control of severe pain.

Methods Aersolised pulmonary fentanyl base 100–300 μg was administered to healthy volunteers using SmartMist™ and the resultant plasma concentration-time data were compared with those from the same doses administered by intravenous (i.v.) injection in the same subjects.

Results Plasma concentrations from SmartMist™ were similar to those from i.v. injection. Time-averaged bioavailability based upon nominal doses averaged ≈100%, and was >50% within 5 min of delivery. Fentanyl systemic pharmacokinetics were similar to those previously reported with no trends to dose-dependence from either route. Side-effects (e.g. sedation, lightheadedness) were the same from both routes.

Conclusions Fentanyl delivery using SmartMist™ can provide analgetically relevant plasma drug concentrations. This, combined with its ease of noninvasive use and transportability, suggests a strong potential for field and domicilliary use, and for patient controlled analgesia without the need for i.v. cannulae.

Keywords: bioavailability, fentanyl, pharmacokinetics, pulmonary administration

Introduction

Several attempts to deliver opioid analgesics by the pulmonary route for systemic action have been reported. Chrubasik and colleagues reported that pulmonary delivery of nebulised morphine could be as effective as intravenous (i.v.) morphine for pain management after abdominal surgery [1] but not after cardiac surgery [2], but they also reported that the bioavailability of nebulised pulmonary morphine was low (mean 17%) [2, 3]. Other studies with nebulised fentanyl have also found that significant pain relief after surgery was possible but, again, that fentanyl serum concentrations were low [4]. Not surprisingly, higher doses of nebulised fentanyl have been found more effective than lower doses when used to treat postoperative pain but the investigators of that study concluded that it was an 'inefficient and awkward way to administer fentanyl' [5]. Others have found that the average bioavailability of a different preparation of inhaled fentanyl was only 12% when compared to the i.v. route [6].

The previous lack of success with pulmonary administration of opioid analgesics appears to be largely due to the inefficiency of the drug delivery systems used. That opioid analgesics can be absorbed from the lung [4–7], and that some therapeutic benefit can be demonstrated, suggests that aerosolised opioids could prove clinically useful given a more effective delivery system. Since the large and highly permeable surface area of the lung is accessible to the inhaled drug during the course of a single inhalation, this route of delivery appears especially useful for drugs requiring a rapid onset of action.

In this study we investigated the feasibility of delivering fentanyl from a novel metered dose inhaler (MDI) in healthy volunteers as a means to achieve analgetically relevant blood concentrations of fentanyl. We used a solution formulation of fentanyl base in a novel breath-actuated accessory (SmartMist™, Aradigm Corporation) [8], that automatically delivered each dose of fentanyl in a single breath only if subjects were inhaling in a manner consistent with pre-programmed parameters.

Methods

These studies were approved by the Human Research Ethics Committee of Royal North Shore Hospital. They were designed to compare the plasma drug concentrations after administration of aerosolised pulmonary (a.p.) fentanyl compared with the same doses delivered intravenously to the same healthy volunteer subjects. The studies were conducted in two phases differentiated by the site of blood sampling for measurement of fentanyl plasma concentrations. The first phase used a peripheral vein for sampling and these experiments are subsequently referred to as 'venous' studies. They consisted of a 1 day dose-ranging study in two subjects (one male and one female), aged 19 and 32 years, with

Correspondence: Professor L. E. Mather, Department of Anaesthesia and Pain Management, University of Sydney at Royal North Shore Hospital, St Leonards, NSW 2065, Australia.

nominal doses of 100 μg, 200 μg and 400 μg fentanyl.* The results were evaluated to ensure that the doses would produce measurable plasma fentanyl concentrations in the systematic studies. The systematic 'venous' study was conducted over 8 weeks in 10 subjects of normal body weight (seven female and three male) aged between 18 and 50 years. The second phase used a peripheral artery for sampling and these experiments are subsequently referred to as 'arterial' studies. These were conducted in five subjects and were performed to supplement the 'venous' studies by way of providing a less damped fentanyl plasma concentration-time response to the drug administration. Subjects enrolled in the 'arterial' study received 100 μg fentanyl i.v. and a.p. doses approximately 1 week apart.

Subjects were recruited via notices placed in university and hospital departments, but were excluded if they had used opioids for chronic pain, were pregnant or lactating, anaemic, obese, or had a history of substance abuse, or significant pulmonary disease. Potential subjects were medically examined and baseline haematological and biochemical blood tests were performed. Those accepted were given a detailed explanation of the study, including potential side-effects and monitoring techniques, and written informed consent was obtained.

Fentanyl formulation and drug delivery system

A prototype novel metered dose oral inhaler accessory (SmartMist™, Aradigm Corporation, Hayward, California, USA) was used; it is a breath-actuated, microprocessor-controlled device that provides the means for measuring and integrating the rate of inspiratory flow. Aerosolised drug is automatically actuated from the device and a single dose of drug delivered when the optimum conditions of flow rate ($45\ l\ min^{-1}$) and inhaled volume (250–500 ml) coincide [8]. Fentanyl was formulated for the MDI as a 5 ml solution of fentanyl base in a 28/72 blend of trichlorofluoromethane and dichlorodifluoromethane containing 0.05% w/w sorbitan trioleate. Each 50 μl metered dose contained 100 μg fentanyl base. The size distribution of fentanyl aerosols was determined after firing 20 successive actuations from primed fentanyl MDIs (one per experiment) into an eight-stage Andersen cascade impactor. The impactor was fitted with a glass 'throat' on top of stage 0 and was operated at an inlet flow-rate of $28.3\ l\ min^{-1}$. The nonvolatile components of the aerosol were quantitatively washed off the actuator, throat and the impactor collection plates using methanol, and the concentration of fentanyl determined by reverse-phase h.p.l.c. From these data, mean (s.d., $n=3$) respirable fraction (i.e. the mass of fentanyl in aerosol droplets <5.8 μm) was determined as 50.3 (1.5)% of the dose metered by each actuation of the valve. The mass median aerodynamic diameter (MMAD) and geometric standard deviation (GSD) of the aerosol entering the cascade impactor were 1.8 μm and 1.9, respectively. Using the method of Cyr *et al.* [9], inter and intra-MDI variation in shot potency (i.e. the amount of fentanyl metered by successive actuations of the MDI) was found to be $<10\%$ of the nominal fentanyl dose (100 μg). When multiple doses were used, the time between doses was ≈ 20 s.

Procedures

The subjects were fasted from midnight of the day before the study. Female subjects underwent a urine pregnancy test on the morning of the study. On arrival in the clinical trials laboratory, subjects were placed in a supine position and monitoring devices applied. A 20-G cannula was placed in a forearm vein for administration of i.v. crystalloid and for i.v. fentanyl administration, when required. In 'venous' studies, a second 16-G Drum-Cartridge® catheter (Abbott Venisystemsô) was advanced via the antecubital fossa of the contralateral arm into the subclavian vein and then fitted with a double three-way stopcock for serial blood sampling. This placement precluded any ambiguities associated with more peripheral blood sampling due to changes in blood flow. Subjects received oxygen ($2\ l\ min^{-1}$) via nasal prongs and ECG, heart rate, blood pressure, respiratory rate, oxygen saturation, and end tidal carbon dioxide were monitored. The subjects were then instructed on the use of the SmartMist™ device and practiced using 'placebo' (saline) inhalant. For pulmonary delivery, subjects exhaled to residual volume, followed by maximal inspiration and breath-holding for a 10 s period.

Preliminary dose-ranging 'venous' studies using 100 μg a.p. fentanyl followed, respectively, by 200 and 400 μg a.p. 20 min apart, were used to ascertain that the doses selected produced measurable plasma fentanyl concentrations. For the systematic 'venous' studies, subjects received a.p. fentanyl on up to four occasions and one or two i.v. fentanyl infusions (3 ml over 1 min) at doses of 100, 200 or 300 μg (Table 1). Venous blood samples were taken immediately before the dose was administered, then at 1, 2, 4, 6, 10, 15, 20, 30 and 40 min, at 20 min intervals to 120 min, and then at 30 min intervals to 720 min after commencement of the dose. It was intended to generate a data set helpful in evaluating inter and intrasubject variability in i.v. and a.p. fentanyl pharmacokinetics, but the set was not completed for various logistical reasons. Analysis of intrasubject variability was therefore not possible. Subsequent analysis was performed on the plasma fentanyl concentration data pooled for each subject/dose as described below. For the 'arterial' study, subjects were prepared as described above except that a 20-G 1.25-inch Vialon® catheter (Insyte® Becton Dickinson) was placed in the radial artery for blood sampling. An arterial blood baseline sample was taken and then 100 μg fentanyl was delivered either as an i.v. bolus dose or by a.p. administration. Arterial blood samples were taken at 1, 2, 5, 10, 15, 20 and 30 min, at 15 min intervals to 90 min, at 30 min intervals to 240 min, and then hourly to a total of 480 min.

Blood samples were centrifuged at $3000\ rev\ min^{-1}$ for 10 min; the plasma was harvested and stored at -20° C until assayed.

Assay of plasma fentanyl concentrations

Plasma fentanyl concentrations were analysed by gas chromatography with a mass spectrometer detector (GC-MS) using

* Nominal fentanyl doses given by inhalation are the amount of drug delivered from the metering valve in the MDI.

Table 1 Pharmacokinetic parameters of fentanyl for all subjects/doses derived from biexponential curve fits to venous fentanyl plasma concentration-time data after intravenous (i.v.) fentanyl administration over 1 min and after aerosolised pulmonary (a.p.) administration.

Route	*Dose*		C_{max} *(ng ml^{-1})*	C_{max}*/mg dose (ng ml^{-1} mg^{-1})*	t_{max} *(min)*	V_c *(l)*	V_{ss} *(l)*	$t_{½,z}$ *(min)*	CL_T *(l min^{-1})*	*AUC/mg dose (ng min ml^{-1} mg^{-1})*	F *(%)*
i.v.	100 μg	Mean	2.8	31	3	58	216	164	1.17	950	
	(*n* = 5)	s.d.	1.5	15	2	36	77	64	0.42	335	
	200 μg	Mean	5.7	29	3	54	223	234	0.78	1326	
	(*n* = 8)	s.d.	4.0	20	1	22	147	128	0.16	288	
	300 μg	Mean	7.2	24	5	39	189	214	0.82	1276	
	(*n* = 4)	s.d.	1.7	6	4	12	74	47	0.21	230	
	Overall	95% CI		20–35¶	2–4¶	40–63	160–265	162–255	0.76–1.05	1046–1361	
a.p.	100 μg	Mean	1.5	15	7			183		924	107
	(*n* = 9)	s.d.	1.5	15	5			101		334	76
	200 μg	Mean	1.9	10	7			384		1137	81
	(*n* = 11)	s.d.	0.5	2	7			328		474	15
	300 μg	Mean	4.2	14	6			231		1641	151⋆
	(*n* = 5)	s.d.	2.7	9	4			72		1440	152⋆
	Overall	95% CI		9–16¶	4–9¶			160–281		872–1451	64–147

C_{max} = maximum measured fentanyl concentration, t_{max} = time of C_{max}, V_c = initial dilution volume, V_{ss} = volume of distribution at steady state equilibrium, $t_{1/2,z}$ = slow half life, CL_T = mean total body clearance, AUC = area under the plasma fentanyl concentration *vs* time curve extrapolated to infinity, F = estimated total bioavailability. ⋆Data from 3 cases, actual values: 44, 84 and 325%. ¶ = significant difference between a.p. and i.v.

selected ion monitoring (SIM) with sufentanil as internal standard, as described in detail elsewhere [10]. Using 1ml plasma samples, the estimated limit of detection of fentanyl was 20 pg ml^{-1}.

Pharmacokinetic analyses

Values of the maximum measured fentanyl concentration (C_{max}) and the time at which C_{max} occurred (t_{max}) were obtained by inspection of the data. Additionally, the serial concentration-time data for each subject at each dose were (adequately) fitted by a biexponential decay curve using Marquardt's weighted nonlinear regression procedure [11]. An exponential term describing a first-order absorption process (K_a) was added for the a.p. administration data. The systemic pharmacokinetic properties of initial dilution volume (V_c), mean total body clearance (CL_T), volume of distribution at steady state equilibrium (V_{ss}) and slow half-life ($t_{1/2,z}$) of fentanyl were calculated for i.v. administration using standard methods [11]. The area under the plasma fentanyl concentration *vs* time curve (AUC) was estimated by the linear trapezoidal method and extrapolated to infinity by adding the integrated terminal washout phase determined from the slow exponential term. The mean bioavailability of a.p. fentanyl was estimated at 5, 20, 60, 180, 360 min and infinity, by dividing the cumulative AUC to that time after i.v. delivery by that after a.p. administration of the same nominal dose. No correction factors were applied for drug delivery ex-device or for respirable fraction. Where multiple tests were performed on the same subject, the plasma concentrations were averaged for each time and dose; the bioavailability of a.p. fentanyl for each subject was estimated from their relevant mean i.v. and a.p. data.

Statistical analysis

Data repeated by subject were analysed using one-way repeated measures analysis of variance (ANOVA) followed by Tukey's test and Student's *t*-tests for paired data, as appropriate. $P<0.05$ was taken as statistically significant.

Results

Dose-ranging 'venous' studies

The fentanyl plasma concentrations of the two subjects participating in the dose-ranging study indicated that

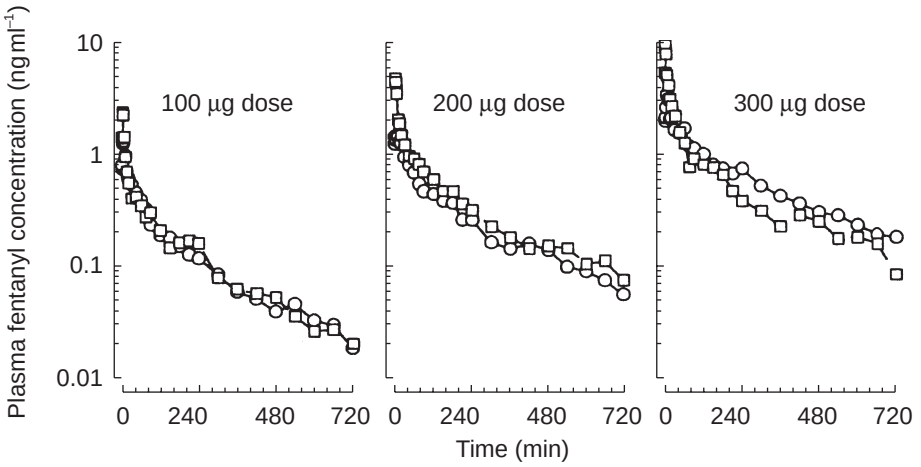

Figure 1 Average fentanyl plasma concentration after 100 μg, 200 μg and 300 μg intravenous (i.v., □) and aerosolised pulmonary (a.p., ○) administrations; error bars have been omitted for clarity.

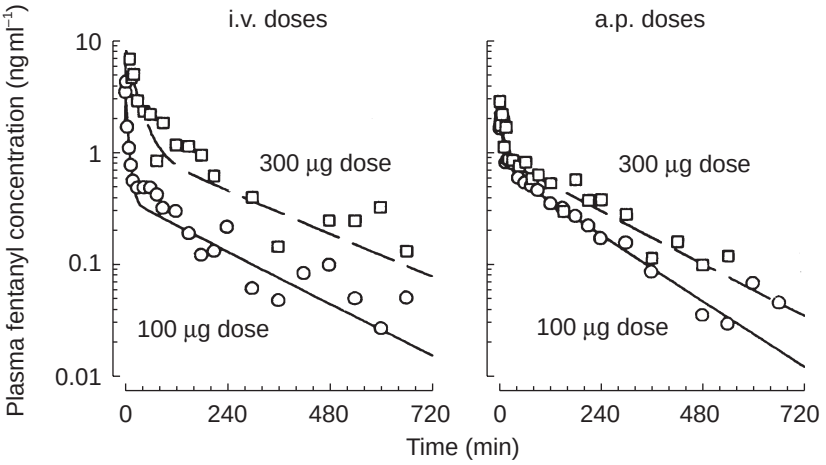

Figure 2 Plasma fentanyl concentrations in one subject (number 2) after intravenous (i.v.) and aerosolised pulmonary (a.p.) doses of 100 and 300 μg fentanyl on separate occasions. Symbols indicate measured concentrations and lines indicate biexponential decay curves of best fit.

analgetically relevant fentanyl plasma concentrations (0.4–3 ng ml^{-1}) could be produced from the (respectively, 100–300 μg) doses used and that the plasma fentanyl concentrations were essentially proportional to dose.

Systematic 'venous' studies

Values of C_{max} and t_{max} are given in Table 1. In four i.v. studies, improbably high fentanyl concentrations (>20 ng ml^{-1}) were found in intrainfusion samples. The probable cause was that the subclavian vein sampling catheter had been advanced into the superior vena cava and had sampled blood enriched with drug while it was being infused into the cephalic vein of the contralateral arm; these values were deleted from subsequent analyses. The catheter was not advanced as far in the remaining studies and the problem did not recur. The respective values of C_{max} and t_{max} analysed across routes indicated that there were no significant differences (paired *t*-tests). However, t_{max} after a.p. administration was significantly greater than that after i.v. administration for the 100 μg and 200 μg doses ($P=0.04$ and $P=0.05$, respectively).

Fentanyl systemic pharmacokinetic parameters after i.v. administration showed no trend with dose (Table 1). The biexponential form of equation acceptably described the time-trend of the pooled data but some individual data sets showed evidence of fluctuations around the trend suggestive of drug 'recycling' (Figure 2). Fentanyl plasma concentration-time data after a.p. administration were acceptably fitted by the same equation, the added first order absorption rate constant made no material difference as t_{max} was near the first sampled point. Again, there was no trend with dose (Table 1).

Across all subjects/doses, the mean values of estimated bioavailability after a.p. administration were 56% at 5 min, 66% at 20 min, 83% at 60 min, 93% at 180 min, 96% at 360 min and 106% at infinite time (Figure 3). There were no apparent dose-related trends in bioavailability or in the rate of bioavailability.

'Arterial' studies

There were no significant differences in C_{max} or t_{max} between i.v. and a.p. administrations. The plasma fentanyl concentration-time data after both routes of administration were again adequately described by a biexponential decay equation; again, a first order absorption rate constant added to the equation for a.p. data made only small improvements to the fit (Figure 4). The systemic pharmacokinetic parameters determined after i.v. administration were not significantly different to those found in the 'venous' studies (Table 2). Variability in plasma fentanyl concentration response to the two routes was similar to that found in the 'venous' studies for both routes.

Side-effects

There were no unexpected side-effects. Subjects reported feelings of sedation, relaxation, difficulty in concentrating, tiredness, lightheadedness, vagueness, mild disorientation, heaviness in limbs, mental slowness and pruritus after both routes of fentanyl administration: these side-effects are typical of fentanyl. Subjects also reported that the a.p. administration left an unpleasant taste and dryness in the mouth. Side-effects and subjective effects generally increased as dose increased.

Discussion

Previous studies of inhaled nebulised fentanyl have been disappointing because of inefficient drug delivery. The present studies clearly indicate that SmartMist™ delivery, using a fine aerosol containing fentanyl base, can provide an efficient and consistent means of delivering the drug via the lungs for its systemic effects. The estimated bioavailability (≈100%) is considerably higher than any previously reported. Moreover, fentanyl was systemically absorbed very rapidly with plasma fentanyl concentrations that were proportional to dose and similar to those following i.v.

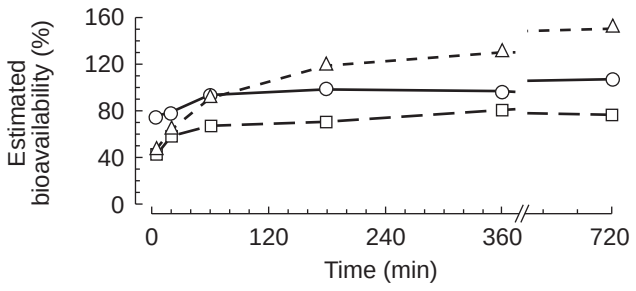

Figure 3 Time-course of the average estimated bioavailability after aerosolised pulmonary administration of three doses of fentanyl (○ 100 μg, □ 200 μg, △ 300 μg) compared with intravenous administration of the same dose to the same subjects on another occasion for the subjects participating in the studies using venous blood sampling; error bars have been omitted for clarity.

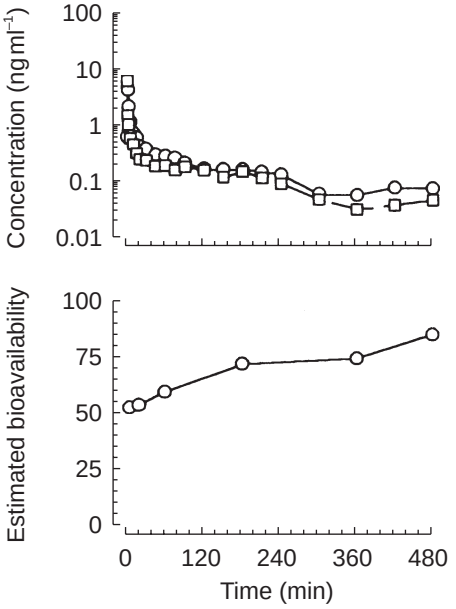

Figure 4 a) average arterial plasma fentanyl concentrations following 100 μg intravenous (□) and 100 μg aerosolised pulmonary (○) administration of fentanyl on a separate occasion. b) time-course of estimated bioavailability after aerosolised pulmonary administration of 100 μg fentanyl.

administration. Hence, plasma fentanyl concentrations following a.p. delivery of clinically reasonable doses were within the range previously reported as analgetically useful for postoperative patients [12], with acceptable variability between subjects (Table 1).

Variability is commonly noted in fentanyl pharmacokinetics [13–15]. Fentanyl has both high tissue solubility and a high clearance. The variability, it would seem, is due to individual and occasional differences in fentanyl clearance and tissue distribution, uncertainty in fentanyl assay and differences in experimental design (especially subjects' physiology/pathophysiology, site and duration of blood sampling, interpretation of pharmacokinetic data). Differences in tissue distribution and regional blood flow can bring about variability in regional, including forearm, venous blood fentanyl concentrations, hence, the 'arterial' studies were performed in an attempt to preclude discrepancy caused by venous blood sampling. Both the 'arterial' and 'venous' studies, nonetheless, led to the same overall results for fentanyl pharmacokinetics with respect to route of administration. Moreover, the overall values for systemic pharmacokinetic parameters found in the i.v. studies are similar to those reported previously for fentanyl [13–15]. Regarding fentanyl assay, this study used a specific assay [10] of better sensitivity and precision than any previously reported; this allowed the fentanyl plasma concentration-time course to be characterized accurately for up to 12 h. As healthy volunteers were used as subjects, the experimental design in this study was uncomplicated by factors related to patient care, including pathology and other medications. The pharmacokinetic data therefore were of high quality and allowed clear and rational conclusions to be drawn.

Fentanyl bioavailability after a.p. administration was assessed as a function of time to give an appreciation of the various stages that might be considered important to onset and duration of action, as well as globally. The overall mean estimated pulmonary bioavailability in the 'venous' study was 90% for 100 μg, 78% for 200 μg and 84% for 300 μg. The estimated pulmonary bioavailability was found to be high, despite the well-known propensity for sequestration in the lungs of blood-borne fentanyl [16–18] and given that no correction factors for respirable fraction or actual delivery were applied to the dose. Although the lungs are rich in drug metabolising enzymes, there was no evidence that fentanyl was being eliminated by the lungs or that uptake of blood-borne fentanyl into lung tissue occurred other than by distribution.

Subjects reported feeling effects of fentanyl immediately following both i.v. and a.p. drug delivery. Clearly, this is the most rapid noninvasive delivery of fentanyl ever reported. The use of a first-order absorption rate constant in the pharmacokinetic model for a.p. administration of fentanyl was not helpful in fitting polyexponential equations to the data. Nevertheless, fentanyl pulmonary absorption probably would be better described by a multiphasic model, whereby a portion of the drug is absorbed extremely rapidly, followed by slower phases in which the remainder of the drug is absorbed over a longer period but this could not be ascribed from the data collected. Many of the plasma fentanyl time curves from both the a.p. and i.v. doses were well-described by the biexponential washout curves but others could be viewed as having secondary peaks consistent with fentanyl 'recycling' (Figure 2). The evidence for fentanyl 'recycling' has been discussed previously in terms of gastric recycling and of altered tissue blood redistribution [13, 14]. In the present studies, the subjects were not required to remain supine for the entire sampling period, often walking about the room; however, a log of activities was not kept which could be associated with secondary peaks. If fentanyl was recycled via the gut contents, then the high hepatic extraction would minimize the recirculated plasma fentanyl concentrations: a similar fate would await fentanyl administered a.p. but swallowed. Nevertheless, there are still no informative data on this issue pertaining to humans. Construction of a more informative model, however, was not feasible from the data collected.

The search for improved noninvasive drug delivery methods for patient controlled analgesia with potent opioids continues. Recent reports of intranasally applied fentanyl [19] suggest that this route might be useful, although the associated pharmacokinetics have not been reported. The results of the present study are extremely encouraging, as they show the highest plasma fentanyl concentrations and greatest bioavailability reported for any study of noninvas-

Table 2 Pharmacokinetic parameters of fentanyl for all subjects and all doses derived from biexponential curve fits to arterial fentanyl plasma concentration-time data after a.p. and i.v. fentanyl administration.

		Estimated					*AUC*	
Route		K_a *(min^{-1})*	V_c *(l)*	V_{ss} *(l)*	$t_{½,z}$ *(min)*	CL_T *(l min^{-1})*	F *(ng ml^{-1} min)*	*(%)*
i.v.	Mean		26	193	131	1.19	87	
($n=4$)	s.d.		18	101	42	0.27	19	
	95% CI		7–44	94–292	89–172	0.93–1.46	68–106	
a.p.	Mean	0.98			204		73	81
($n=5$)	s.d.	0.86			149		23	32
	95% CI	0.2–1.7			74–335		53–94	50–113

Estimated K_a = estimated first-order pulmonary absorption rate constant, V_c = initial dilution volume, V_{ss} = volume of distribution at steady state equilibrium, $t_{1/2,z}$ = slow half life, CL_T = mean total body clearance, AUC = area under the plasma fentanyl concentration *vs* time curve extrapolated to infinity, F = estimated total bioavailability.

ively delivered fentanyl. Subjects found the technology easy to use and had little difficulty in getting the device to deliver drug after practice. While these studies still should be regarded as preliminary, the results suggest that the SmartMist™ delivery system can provide an efficient, readily portable, noninvasive means of delivering fentanyl that could prove therapeutically useful.

The authors are pleased to acknowledge the nursing skills of Ms I. de Jong, the analytical skills of Ms B. Fryirs and the financial support of Aradigm Corporation in performing this study. We are also indebted to Anthony Rowe, Welsh School of Pharmacy, University of Wales, Cardiff for developing and providing the fentanyl MDIs used in the study.

References

1 Chrubasik J, Geller E, Niv D, Zindler M. Morphine inhalation versus intravenous infusion in pain treatment after abdominal surgery. *Anesth Analg* 1987; **66**: S29.

2 Chrubasik S, Chrubasik J, Friedrich G, *et al*. Postoperative treatment by means of a morphine aerosol: A multicenter study. In *Advances in Pain Therapy II*, eds Chrubasik J, Cousins M, Martin E, Heidelberg: Springer-Verlag, 1993: 151–167.

3 Chrubasik J, Wüst H, Friedrich G, Geller E. Absorption and bioavailability of nebulized morphine. *Br J Anaesth* 1988; **61**: 228–230.

4 Worsley MH, Macleod AD, Brodie MJ, Asbury AJ, Clark C. Inhaled fentanyl as a method of analgesia. *Anaesthesia* 1990; **45**: 449–451.

5 Higgins MJ, Asbury AJ, Brodie MJ. Inhaled nebulised fentanyl for postoperative analgesia. *Anaesthesia* 1991; **46**: 973–976.

6 Hung OR, Whynot SC, Varvel JR, Shafer SL, Mezei M. Pharmacokinetics of inhaled liposome-encapsulated fentanyl. *Anesthesiology* 1995; **83**: 277–284.

7 Masters N, Heap G, Wedly J, Moore A. Inhaled nebulised morphine and diamorphine: useful in general practice? *The Practitioner* 1988; **232**: 910–914.

8 Farr SJ, Rowe AM, Rubsamen R, Taylor G. Aerosol deposition in the human lung following administration from a microprocessor controlled pressurised metered dose inhaler. *Thorax* 1995; **50**: 639–644.

9 Cyr TD, Graham SJ, Li KYR, Lovering EG. Low first spray content in albuterol metered-dose inhalers. *Pharm Res* 1991; **8**: 658–660.

10 Fryirs B, Woodhouse A, Huang JL, Dawson M, Mather LE. Determination of subnanogram concentrations of fentanyl in plasma by gas chromatography mass spectrometry—comparison with standard radioimmunoassay. *J Chromatogr B Biomed Appl* 1997; **688**: 79–85.

11 Sebalt RJ, Kreeft JH. Efficient pharmacokinetic modeling of complex clinical dosing regimens; the universal elementary dosing regimen and computer algorithm EDFAST. *J Pharm Sci* 1987; **76**: 93–100.

12 Gourlay GK, Kowalski SR, Plummer JL, Cousins MJ, Armstrong PJ. Fentanyl blood concentration—analgesic response relationship in the treatment of postoperative pain. *Anesth Analg* 1988; **67**: 329–337.

13 Mather LE. Pharmacokinetics of fentanyl and its newer derivatives. *Clin Pharmacokin* 1983; **8**: 422–446.

14 Mather LE, Gourlay GK. Pharmacokinetics of fentanyl. In *Transdermal fentanyl* eds Lehmann KA, Zech D, Heidelberg: Springer-Verlag, 1992: 73–97.

15 Reilly CS, Wood AJJ, Wood M. Variability of fentanyl pharmacokinetics in man. Computer predicted plasma concentrations for three intravenous dosage regimens. *Anaesthesia* 1984; **40**: 837–843.

16 Roerig DL, Kotrly KJ, Vucins EJ, Ahlf SB, Dawson CA, Kampine JP. First pass uptake of fentanyl, meperidine, and morphine in the human lung. *Anesthesiology* 1987; **67**: 466–472.

17 Roerig DL, Kotrly KJ, Ahlf SB, Dawson CA, Kampine JP. Effect of propranolol on the first pass uptake of fentanyl in the human and rat lung. *Anesthesiology* 1989; **71**: 62–68.

18 Boer F. *Pulmonary uptake of opioids*. PhD thesis: University of Leiden 1994: 65–75.

19 Striebel HW, Oelmann T, Spies C, Rieger A, Schwagmeier R. Patient-controlled intranasal analgesia: A method for noninvasive postoperative pain management. *Anesth Analg* 1996; **83**: 548–551.

(*Received 23 September 1997, accepted 29 January 1998*)

